

(19)



Europäisches Patentamt  
European Patent Office  
Office européen des brevets

(11) Publication number:

**0 102 404**  
**A1**

(12)

# EUROPEAN PATENT APPLICATION

(21) Application number: 82108105.6

(51) Int. Cl.<sup>3</sup>: **C 07 D 231/54**  
**A 61 K 31/415**

(22) Date of filing: 02.09.82

(43) Date of publication of application:  
14.03.84 Bulletin 84/11

(84) Designated Contracting States:  
BE CH DE FR GB IT LI LU NL SE

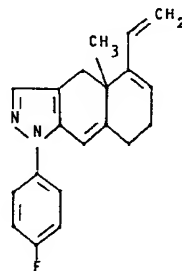
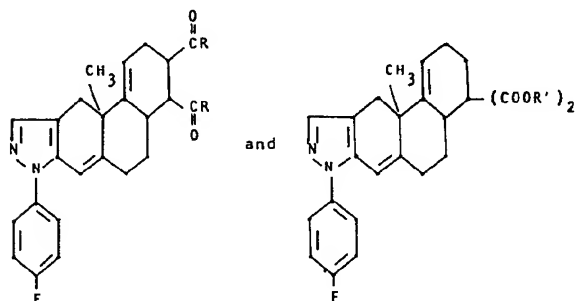
(71) Applicant: **STERLING DRUG INC.**  
90 Park Avenue  
New York New York(US)

(72) Inventor: **Bell, Malcolm Rice**  
R.D. 1 Box 156A  
East Greenbush New York(US)

(74) Representative: **Ballie, Iain Cameron et al,**  
c/o Ladas & Parry Isartorplatz 5  
D-8000 München 2(DE)

(54) Novel polycyclic fused pyrazole compounds useful as antiinflammatory agents and preparation thereof.

(57) The compounds of the formulas



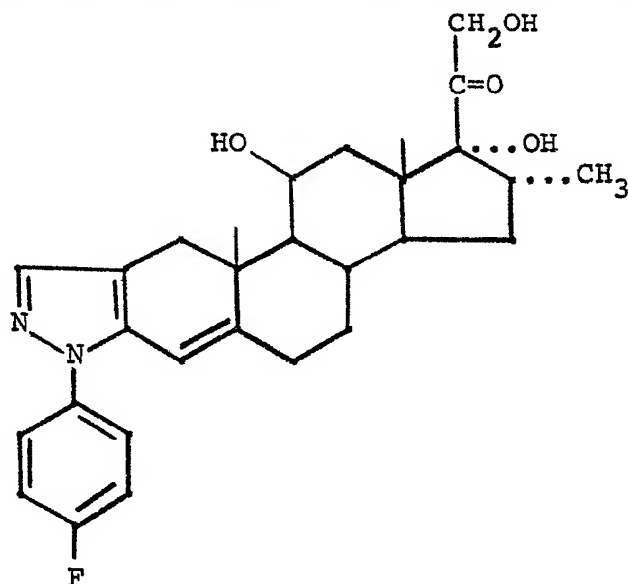
with the appropriate dienophile.

where R and R' are lower-alkyl possess glucocorticoid activity, and are prepared by reacting the compound of the formula

EP 0 102 404 A1

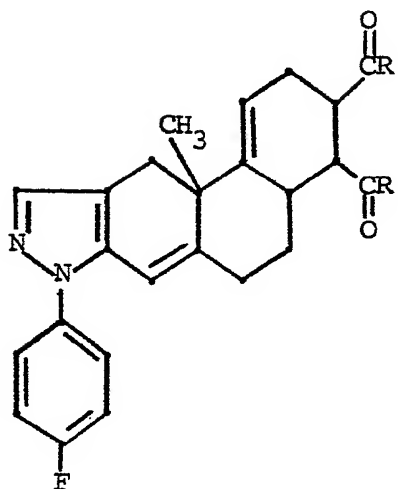
The present invention relates to novel polycyclic fused pyrazole compounds, useful as anti-inflammatory agents, and the preparation thereof.

Typical glucocorticoid activity is rarely found  
5 in structures which do not possess an intact steroid nucleus. Such activity is found in naturally occurring steroids such as cortisone, hydrocortisone and aldosterone, as well as numerous synthetic modifications thereof, all containing the intact steroid nucleus. An example of a synthetic  
10 cortical steroid having high activity is a fluorophenylpyrazole derivative reported by Fried et al., J. Am. Chem. Soc. 85, 236 (1963), having the structure



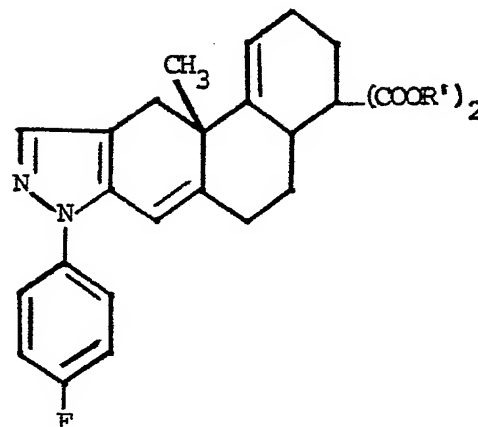
-2-

The present invention relates to compounds having the formulas:



I

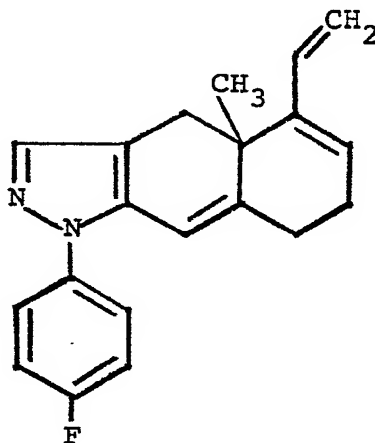
and



II

wherein R and R' are lower-alkyl groups. Said compounds  
 5 can be used in a pharmaceutical composition for treating  
 inflammation in mammals which comprises an anti-inflammatorily  
 effective amount of said compound of Formula I or II and a  
 pharmaceutically acceptable carrier. One can reduce  
 inflammation in a mammal by administering to said mammal  
 10 an anti-inflammatorily effective amount of a compound of  
 Formula I or II.

The invention also relates to an intermediate for  
 use in the preparation of the compounds of Formulas I and II,  
 said intermediate having the formula:



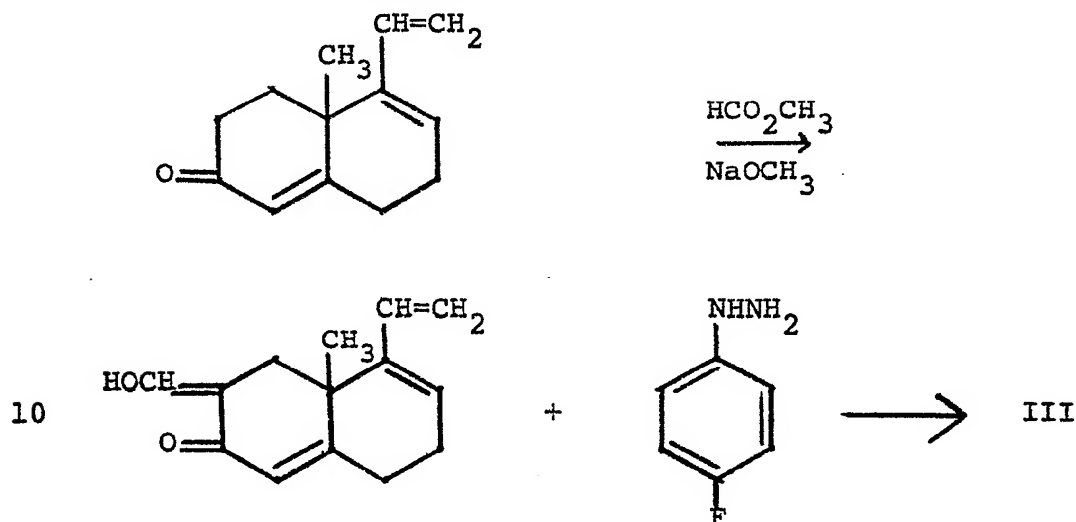
III

15

-3-

One can prepare the compounds of Formulas I or II by reacting the compound of Formula III with a compound of the formula  $\text{RCOCH=CHCOR}$  or  $\text{CH}_2=\text{C}(\text{COOR}')_2$ , respectively.

The novel intermediate of Formula III is prepared from a known starting material, 5-ethenyl-4,4a,7,8-tetrahydro-4a-methyl-2(3H)-naphthalenone (cf. Bell et al. U.S. Patent 4,157,349, June 5, 1979) in accordance with the following reactions:



The trienone starting material is reacted with methyl formate in the presence of sodium methoxide in an inert solvent such as tetrahydrofuran to afford 5-ethenyl-3-hydroxymethylene-4,4a,7,8-tetrahydro-4a-methyl-2(3H)-naphthalenone, and the latter is then reacted with 4-fluorophenylhydrazine or an acid-addition salt thereof in the presence of acetic acid to give the compound of Formula III.

The preparation of a compound of Formula I by reacting the compound of Formula III with an unsaturated diketone of the formula  $\text{RCOCH=CHCOR}$  takes place by heating the reactants in an inert solvent at a temperature between about 50° and 150°C. Similarly, a compound of Formula II is prepared by heating III with a di-lower-alkyl methylenemalonate  $[\text{CH}_2=\text{C}(\text{COOR}')_2]$ . In order to suppress the tendency of the diene to polymerize, a small quantity of a free radical chain reaction inhibitor such as 1,2,3-

-4-

benzenetriol (pyrogallol), may be added.

The lower-alkyl groups R and R' preferably have from one to four carbon atoms, including, for example, methyl, ethyl, propyl, isopropyl, butyl and isobutyl.

5           The compounds of Formulas I and II exhibit an endocrinological profile characteristic of compounds possessing glucocorticoid properties and systemic and/or topical anti-inflammatory activity; cf. R.H. Silber, The Biology of Anti-inflammatory Steroids, Annals of the  
10 New York Academy of Sciences, Vol. 82, Art. 4. pp. 821-828.

When the compounds of Formulas I and II are administered orally to rats they cause a significant depression in thymus weight, adrenal weight and body weight gain without a change in food consumption.

15           The compound of Formula I where R is methyl has also been found to possess oral glucocorticoid activity by the liver glycogen deposition test and anti-inflammatory activity by the  $\alpha$ -tocopherol pouch test in rats.

The test procedures used to determine the  
20 biological activities of the compounds of the invention were carried out as follows:

Endocrine Profile: Mature female rats with an average body weight of 202 g and a body weight range of 15 g or less were medicated orally with test compound for 2 weeks. The  
25 test compound was prepared as a solution or suspension in 1% gum tragacanth or 0.75% methyl cellulose. On the day following the last medication, the rats were killed and the thymus and adrenal of each rat were removed, cleaned, and weighed. Body weights and food consumptions were also  
30 recorded.

Anti-inflammatory Activity ( $\alpha$ -tocopherol pouch test):  
Male rats which weighed 120 g were selected for testing. A rapid subcutaneous injection of 25 mL of air was made between the scapulae of each rat. This resulted in the  
35 establishment of an airfilled pouch into which 0.5 mL of dl- $\alpha$ -tocopherol was injected. The test compound was administered in daily oral doses for 7 days beginning on

-5-

the day of pouch formation. The compound to be tested was suspended in 1% gum tragacanth. Twenty-four hours after the last medication, the pouches were dissected free, and the fluid volume was measured. The inhibition of liquid exudate is a measure of the anti-inflammatory activity.

Glycogenic Activity: Mature male rats were bilaterally adrenalectomized 5 days prior to the test. These rats were medicated orally with the test compound for 5 days. Seven hours after the last medication, the rats (which have been fasted overnight) were anesthetized with sodium pentobarbital and a portion of one lobe of the liver was removed and frozen on dry ice for subsequent glycogen determination.

The compounds of the invention can be formulated for topical application by solution or dispersion in a conventional pharmaceutically acceptable liquid, cream or ointment base. The effective ingredient is preferably present in a concentration of 0.01% to 5.0% by weight.

The compounds of the invention can be formulated for oral administration in tablet or capsule form with conventional excipients. The active ingredient is preferably present in an amount of 1 mg to 100 mg per unit dosage form.

The following examples will further illustrate the invention.

25 Example 1

(a) 5-Ethenyl-3-hydroxymethylene-4,4a,7,8-tetrahydro-4a-methyl-2(3H)-naphthalenone.

A solution of 50.0 g (0.265 mol) of 5-ethenyl-4,4a,7,8-tetrahydro-4a-methyl-2(3H)-naphthalenone in 350 mL of tetrahydrofuran was cooled to -5°C. in an ice-methanol bath and stirred under nitrogen while 57.2 g (1.06 mol) of sodium methoxide was added. The resulting mixture was stirred for 30 min at -5°C. and then a solution of 114 mL (1.85 mol) of methyl formate in 100 mL of tetrahydrofuran was added slowly. The mixture was stirred overnight at room temperature and then poured onto a mixture of ice-water (1500 mL) and 6N hydrochloric acid (265 mL). The

-6-

product was extracted with ether and the combined extracts were washed with water. The dried extract was dried over anhydrous magnesium sulfate and concentrated in vacuo to afford an oil. This oil was triturated with hexane

5 (4 x 250 mL) and the combined triturates were dried over magnesium sulfate and concentrated in vacuo to afford 55.37 g of a red oil, consisting essentially of the above-entitled compound as established by proton NMR (PMR) spectral data.

(b) 1-Ethenyl-6-(4-fluorophenyl)-3,4,9,9a-tetrahydro-9a-methyl-6H-naphtho [2,3-c]pyrazole (III).

4-Fluorophenylhydrazine hydrochloride (45.85 g, 0.282 mol) and sodium acetate (23.14 g, 0.282 mol) were added to a solution of 55.37 g (0.256 mol) of the product obtained in part (a) above in 225 mL of glacial acetic acid.

15 The mixture was stirred overnight at room temperature and then concentrated in vacuo to afford a semi-solid. This material was suspended in ether (1 L) and filtered to remove sodium chloride. The ether filtrate was washed with water (4 x 250 mL), saturated sodium bicarbonate (until weakly  
20 basic) and saturated sodium chloride (100 mL). The extract was dried over anhydrous magnesium sulfate, decolorized with charcoal and concentrated in vacuo to afford an oil. This oil was triturated with 1:2 ether-hexane (3 x 750 mL) to afford 69.58 g of a dark brown oil. An analytical sample  
25 was prepared by using high-performance liquid chromatography with 1:3 ether-hexane as solvent. The resulting yellow oil was triturated with pentane to afford 1-ethenyl-6-(4-fluorophenyl)-3,4,9,9a-tetrahydro-9a-methyl-6H-naphtho [2,3-c]pyrazole as a yellow solid, m.p. 70-72°C., with a  
30 consistent PMR spectrum.

#### Example 2

1,1'-[8-(4-Fluorophenyl)-2,3,4,4a,5,6,11,11a-octahydro-11a-methyl-8H-phenanthro [2,3-c]pyrazole-3,4-diyl]bis[ethanone]  
(I; R = CH<sub>3</sub>).

35 A solution of 20 g (0.065 mol) of 1-ethenyl-6-(4-fluorophenyl)-3,4,9,9a-tetrahydro-9a-methyl-6H-naphthol [2,3-c]-pyrazole in 200 mL benzene and 8.07 g (0.072 mol)

-7-

of 3-hexene-2,5-dione was stirred at reflux for 40 hours under nitrogen. The cooled reaction mixture was filtered through silica gel and concentrated in vacuo. The resultant oil was triturated with ether to afford 7.54 g of a gold solid as a mixture of isomers, m.p. 138-142°C., as determined by PMR spectroscopy. Five g of this mixture of isomers was separated using high-performance liquid chromatography with 1:4 ethyl acetate-hexane. The major isomer was recrystallized from CH<sub>2</sub>Cl<sub>2</sub>-isooctane to afford 3.0 g of 1,1'-[8-(4-fluorophenyl)-2,3,4,4a,5,6,11,11a-octahydro-11a-methyl-8H-phenanthro[2,3-c]pyrazole-3,4-diyl]bis[ethanone], a white solid, m.p. 157-159°C., a single isomer as determined by PMR spectroscopy.

In the endocrine profile determination, Compound I (R = CH<sub>3</sub>) at a dose level of 5 mg/kg caused a 59% reduction in weight of the thymus, 40% reduction in adrenal weight and 80% reduction in body weight gain as compared with the controls. In the  $\alpha$ -tocopherol pouch test, Compound I (R = CH<sub>3</sub>) was active with ED<sub>50</sub> = 23 mg/kg. In the glycogenic activity test, Compound I (R = CH<sub>3</sub>) at dose levels of 9 and 27 mg/kg/day  $\times$  5 produced liver glycogen deposition values of  $9.42 \pm 0.65$  and  $25.48 \pm 3.39$  mg/g of tissue, respectively, as compared to  $1.75 \pm 0.04$  mg/g for the vehicle (ethanol: cottonseed oil 1:9 v/v) alone.

By replacing the 3-hexene-2,5-dione in the procedure of Example 2 by a molar equivalent amount of 4-octene-3,6-dione, 5-decene-4,7-dione or 6-dodecene-5,8-dione, it is contemplated that there can be obtained 1,1'-[8-(4-fluorophenyl)-2,3,4,4a,5,6,11,11a-octahydro-11a-methyl-8H-phenanthro[2,3-c]pyrazole-3,4-diyl]bis[propanone] (I; R = CH<sub>2</sub>CH<sub>3</sub>), 1,1'-[8-(4-fluorophenyl)-2,3,4,4a,5,6,11,11a-octahydro-11a-methyl-8H-phenanthro[2,3-c]pyrazole-3,4-diyl]bis[butanone] (I; R = CH<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>), or 1,1'-[8-(4-fluorophenyl)-2,3,4,4a,5,6,11,11a-octahydro-11a-methyl-8H-phenanthro[2,3-c]pyrazole-3,4-diyl]bis[pentanone] (I; R = CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>), respectively.



Example 3

Diethyl 8-(4-fluorophenyl)-2,3,4,4a,5,6,11,11a-octahydro-11a-methyl-8H-phenanthro[2,3-c]pyrazole-4,4-dicarboxylate (II; R = CH<sub>2</sub>CH<sub>3</sub>).

5           A solution of 25.81 g (0.084 mol) of 1-ethenyl-6-(4-fluorophenyl)-3,4,9,9a-tetrahydro-9a-methyl-6H-naphtho[2,3-c]-pyrazole, 18.1 g (0.105 mol) of diethyl methylenemalonate and 500 mg of 1,2,3-benzenetriol in 200 mL of xylene was refluxed for 20 hours. The cooled reaction  
10 mixture was filtered through silica gel and concentrated in vacuo to afford 41.93 g of a brown oil. The oil was purified by using high-performance liquid chromatography with 3.97 ethyl acetate-CH<sub>2</sub>Cl<sub>2</sub> followed by recrystallization from methanol to afford 10.98 g of diethyl 8-(4-fluoro-  
15 phenyl)-2,3,4,4a,5,6,11,11a-octahydro-11a-methyl-8H-phenanthro-[2,3-c]pyrazole-4,4-dicarboxylate as a colorless solid, m.p. 133-135°C. The PMR spectrum was consistent with the assigned structure.

          In the endocrine profile determination, Compound II  
20 (R = CH<sub>2</sub>CH<sub>3</sub>) at a dose level of 100 mg/kg caused an 80% reduction in thymus weight, 47% reduction in adrenal weight and 186% reduction in body weight gain as compared with the controls. Compound II (R = CH<sub>2</sub>CH<sub>3</sub>) was inactive in the α-tocopherol pouch test at 100 mg/kg.

25           By replacing the diethyl methylenemalonate in the procedure of Example 3 by a molar equivalent amount of dimethyl methylenemalonate, dipropyl methylenemalonate or dibutyl methylenemalonate, it is contemplated that there can be obtained dimethyl 8-(4-fluorophenyl)-2,3,4,4a,5,6,  
30 11,11a-octahydro-11a-methyl-8H-phenanthro[2,3-c]pyrazole-4,4-dicarboxylate (II; R = CH<sub>3</sub>), dipropyl 8-(4-fluorophenyl)-2,3,4,4a,5,6,11,11a-octahydro-11a-methyl-8H-phenanthro[2,3-c]pyrazole-4,4-dicarboxylate (II; R = CH<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>), or dibutyl 8-(4-fluorophenyl)-2,3,4,4a,5,6,11,11a-octahydro-11a-methyl-  
35 8H-phenanthro[2,3-c]pyrazole-4,4-dicarboxylate (II; R = CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>), respectively.

-1-

C L A I M S

1. A compound having the Formula I or II (herein) wherein R and R' are each lower-alkyl.
2. 1,1'-[8-(4-Fluorophenyl)-2,3,4,4a,5,6,11,11a-octahydro-11a-methyl-8H-phenanthro[2,3-c]pyrazole-3,4-diyl]bis-[ethanone], according to claim 1.
3. Diethyl 8-(4-fluorophenyl)-2,3,4,4a,5,6,11,11a-octahydro-11a-methyl-8H-phenanthro[2,3-c]pyrazole-4,4-dicarboxylate, according to claim 1.
4. A process for preparing a compound according to claim 1, which comprises reacting 1-ethenyl-6-(4-fluorophenyl)-3,4,9,9a-tetrahydro-9a-methyl-6H-naphtho[2,3-c]pyrazole with a compound of the formula  $\text{RCOCH=CHCOR}$  or  $\text{CH}_2=\text{C}(\text{COOR}')_2$ .
5. A process according to claim 4, for preparing the compound according to claim 2, which comprises reacting 1-ethenyl-6-(4-fluorophenyl)-3,4,9,9a-tetrahydro-9a-methyl-6H-naphtho[2,3-c]pyrazole with 3-hexene-2,5-dione.
6. A process according to claim 4, for preparing the compound according to claim 3, which comprises reacting 1-ethenyl-6-(4-fluorophenyl)-3,4,9,9a-tetrahydro-9a-methyl-6H-naphtho[2,3-c]pyrazole with diethyl methylenemalonate.
7. 1-Ethenyl-6-(4-fluorophenyl)-3,4,9,9a-tetrahydro-9a-methyl-6H-naphtho[2,3-c]pyrazole having the Formula III (herein).
8. A pharmaceutical composition for treating inflammation in mammals which comprises an anti-inflammatorily effective amount of a compound according to any one of claims 1-3, and a pharmaceutically acceptable carrier.



European Patent  
Office

# EUROPEAN SEARCH REPORT

0102404

Application number

EP 82 10 8105

DOCUMENTS CONSIDERED TO BE RELEVANT			
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. Cl. *)
X	US-A-4 307 102 (M.R. BELL) * Whole document *	4-7	C 07 D 231/54 A 61 K 31/415
X	--- EP-A-0 058 841 (STERLING DRUG) * Page 8; claims * -----	4-7	
			TECHNICAL FIELDS SEARCHED (Int. Cl. *)
			C 07 D 231/00
The present search report has been drawn up for all claims			
Place of search THE HAGUE		Date of completion of the search 21-06-1983	Examiner CREMERS K.
<b>CATEGORY OF CITED DOCUMENTS</b>			
X : particularly relevant if taken alone Y : particularly relevant if combined with another document of the same category A : technological background O : non-written disclosure P : intermediate document		T : theory or principle underlying the invention E : earlier patent document, but published on, or after the filing date D : document cited in the application L : document cited for other reasons & : member of the same patent family, corresponding document	